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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/088,952	03/22/2002	Stephen H. Leppla	15280-4051US	4741

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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 04/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 10/088,952	**Applicant(s)** LEPPLA ET AL.	
	Examiner Brandon J. Fetterolf, PhD	**Art Unit** 1642	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 28 February 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☒ The Notice of Appeal was filed on *2/26/2006*. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: *7*.
   Claim(s) rejected: *1,4,8,9,11-14,18-22 and 25-30*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☒ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see attached.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER

Response to the Amendment

The Amendment filed on 02/28/2006 in response to the previous Final Office Action (08/23/2005) is acknowledged and has been entered.

Claims 1, 4, 7-9, 11-14, 18-22 and 25-30 are currently pending and under consideration.

The Declaration by Dr. Stephen H. Leppla under 37 CFR 1.132 filed on 02/28/2006 is insufficient to overcome the rejection of claims 1, 4, 8, 11-14, 18-22 and 25-30 under 35 U.S.C. 103(a) based upon being unpatentable over Leppla et al. (IDS, 1997) in view of Bayley *et al.* (IDS, 1998) as set forth in the last Office action because: Applicant has not provided a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. *See* CFR 1.116 (e)

As such, Applicants arguments, which incorporate the Declaration by Dr. Stephen H. Leppla have not been considered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Rejections Maintained:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4, 8-9, 11-14, 18-22 and 25-29 **remain** rejected and **new** claim 30 is rejected under 35 U.S.C. 103(a) as being unpatentable over Leppla et al. (IDS, 1997) in view of Bayley *et al.* (IDS, 1998).

Leppla *et al.* teach (column 115, lines 410-63) a method for targeting compounds having a desired biological activity not present on native anthrax lethal factor (LF) to a specific cell population, comprising: a) administering to the cell population a first compound comprising a first protein consisting essentially of: i) the translocation domain and the anthrax lethal factor (LF) binding domain of the native anthrax protective antigen (PA) protein, and ii) a ligand domain that specifically binds the first protein to a target on the surface of the cell population to bind the first compound to said surface; and b) administering to the resultant cell population a second compound comprising a fusion protein or conjugate consisting essentially of: i) the anthrax protective antigen (PA) binding domain of the native anthrax lethal factor (LF) protein, chemically attached to ii) a biological activity-inducing polypeptide to bind the second compound to the first compound on the surface of the cell population, internalize the second compound into the cell population, and effect the activity of the polypeptide therein. The patent further teaches (Column 116, lines 42-44, 53-56, and 63-64) that the ligand domain of the first compound can be either the ligand domain of the native anthrax protective antigen (PA) protein or growth factor, or an antibody, wherein the antibody is a single chain antibody. Furthermore, Leppla *et al.* disclose (column 115, lines 64-67 and column 116, lines 40-41) that the anthrax protective antigen (PA) binding domain of the second compound comprising at least the first 254 amino acid residues but less than all of the amino acid residues of the native anthrax lethal factor. Moreover, the patent teaches (column 116, lines 51-52) that the second compound may comprise the anthrax protective antigen (PA) binding domain of the native anthrax lethal factor (LF) protein chemically attached to a polypeptide through a peptide bond. In addition, Leppla *et al.* teach (column 116, lines 49-52 and 57-62) that the polypeptide of the second compound is an enzyme or a toxin, wherein the toxin can be Pseudomonas exotoxin A (PE), A chain of Diptheria toxin, or shiga toxin. With regards to Pseudomonas exotoxin A, the patent teaches (column 17, lines 15+) that anthrax lethal toxin is linked to the ADP-Ribosylation Domain of Pseudomonas exotoxin. Leppla *et al.* also disclose (Abstract, last sentence) proteins including an anthrax protective antigen which has been mutated to replace the trypsin cleavage site with residues recognized specifically by the HIV-1 protease. Specifically, the patent teaches (column, 11, lines 10-13) PA proteins which have been mutated to replace R164 to 167 with an amino acid sequence recognized by the HIV-1 protease. In addition, the patent teaches (column 1, lines 24-26) that in a therapeutic or diagnostic setting, the used of an sFv may offer attractive

advantages over the use of monoclonal antibodies. Lastly, Leppla *et al.* teach (column 15, lines 27-37) that this methodology can be used to specifically killing a tumor cell in a subject.

Leppla *et al.* does not disclose a mutated protective antigen comprising a plasminogen activator-recognized cleavage site in place of the native protective antigen furin-recognized cleavage site.

Bayley *et al.* teach (column 12, lines 13+) the construction of Ab-αHL conjugates and mutated two chain αHL conjugates, wherein a protease can be employed as an activator of inactive compounds, e.g. plasminogen activator, specifically urokinase-type plasminogen activator (uPA). Specifically, the patent teaches (column 12, lines 13+) that because cancer cells have been shown to secrete plasminogen activator, the protease cleavage site for plasminogen activator can be incorporated into the conjugate for specific activation of this cell type.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to incorporate a plasminogen activator-protease cleavage site in place of the native protective antigen furin-recognized cleavage site as a way of targeting a compound to a cancer cell over-expressing a plasminogen activator or plasminogen activator receptor. One would have been motivated to make this substitution because Bayley *et al.* teach that it is well known in the art that a plasminogen activator, such as uPA, can be employed as an activator of an inactive agent such as the protective antigen protein of Leppla *et al.*. One of ordinary skill in the art would have reasonable expectation of success that by combining the plasminogen activator-recognized cleavage site of Bayley *et al.* with the method of specifically targeting a bioactive compound taught by Leppla *et al.*, one would achieve a method of specifically targeting a compound to a cancer cell because as evidenced by Bayley et al., cancer cells have been shown to secrete plasminogen activator.

In response to this rejection, Applicants contend that the cited references alone or in combination do not render the presently claimed invention obvious. Applicants assert that as set for in the Declaration of Dr. Leppla, one of skill in the art would not have a reasonable expectation of success to practice the claimed invention based on the cited references because the disclosure of Bayley et al. that a uPA cleavage site can be incorporated into a polypeptide does not remedy the deficiency in Leppla et al. Applicants further submit that as Dr. Leppla explains, even if one of skill in the art were to combine the disclosures of Leppla et al. and Bayley et al. there would be no reasonable expectation of success in being able to practice the presently claimed methods (see,

Declaration, ¶ 7). Moreover, Applicants argue that the present invention is the first to demonstrate that a mutant protective antigen can be used to deliver a compound to a cell overexpressing uPA (see, Declaration, ¶ 7). Furthermore, Applicants contend that one of skill in the art would not have expected that the uPA expressed on the surface of a target cell and the uPA cleavage site on the mutant protective antigen would have come into contact with each other (see, Declaration, ¶ 7). For example, Applicants assert that the uPA cleavage site in the mutant PA might not be positioned at an appropriate distance from the cell membrane to contact the uPA on the surface of the target cell (see, Declaration, ¶ 7). In addition, Applicants argue point out that the experimental evidence presented in Dr. Leppla's declaration demonstrates that the claimed methods are surprisingly effective. More specifically, Applicants assert that the mutant protective antigens of the presently claimed invention are particularly effective for delivering a compound to target cells, as described in the experiments reported in the Leppla Declaration and in Rono et al. (Mol. Cancer Ther. 2006; 5 (1): 89-96).

As Applicant's arguments appear to be solely drawn to the Declaration by Dr. Leppla, such arguments have not been considered.

Conclusion

Claim 7 is objected to as being dependent from rejected independent claim 1. In the instant case, the prior art does not appear to suggest that the plasminogen activator recognized cleavage site is SEQ ID NO: 5.

All other rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brandon J Fetterolf, PhD
Examiner
Art Unit 1642

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